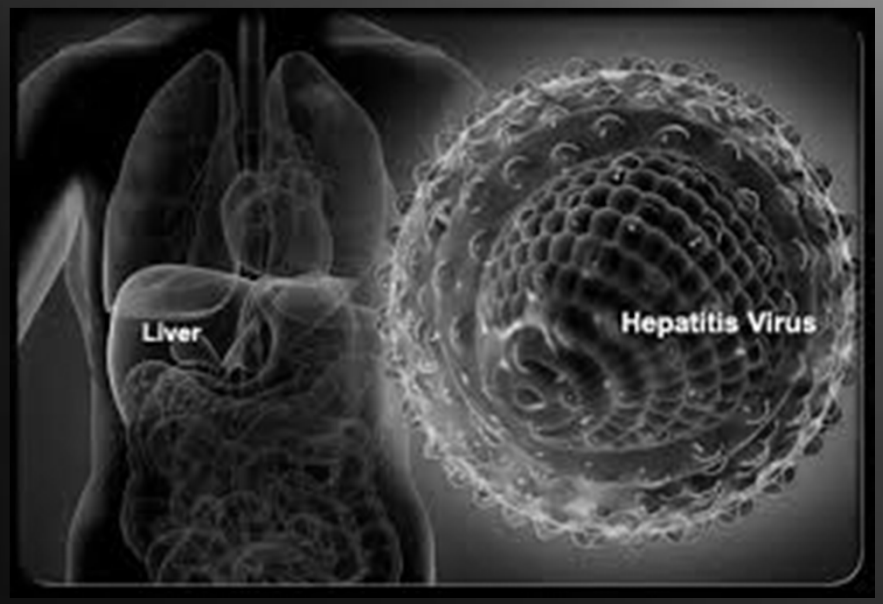
Acute viral hepatitis



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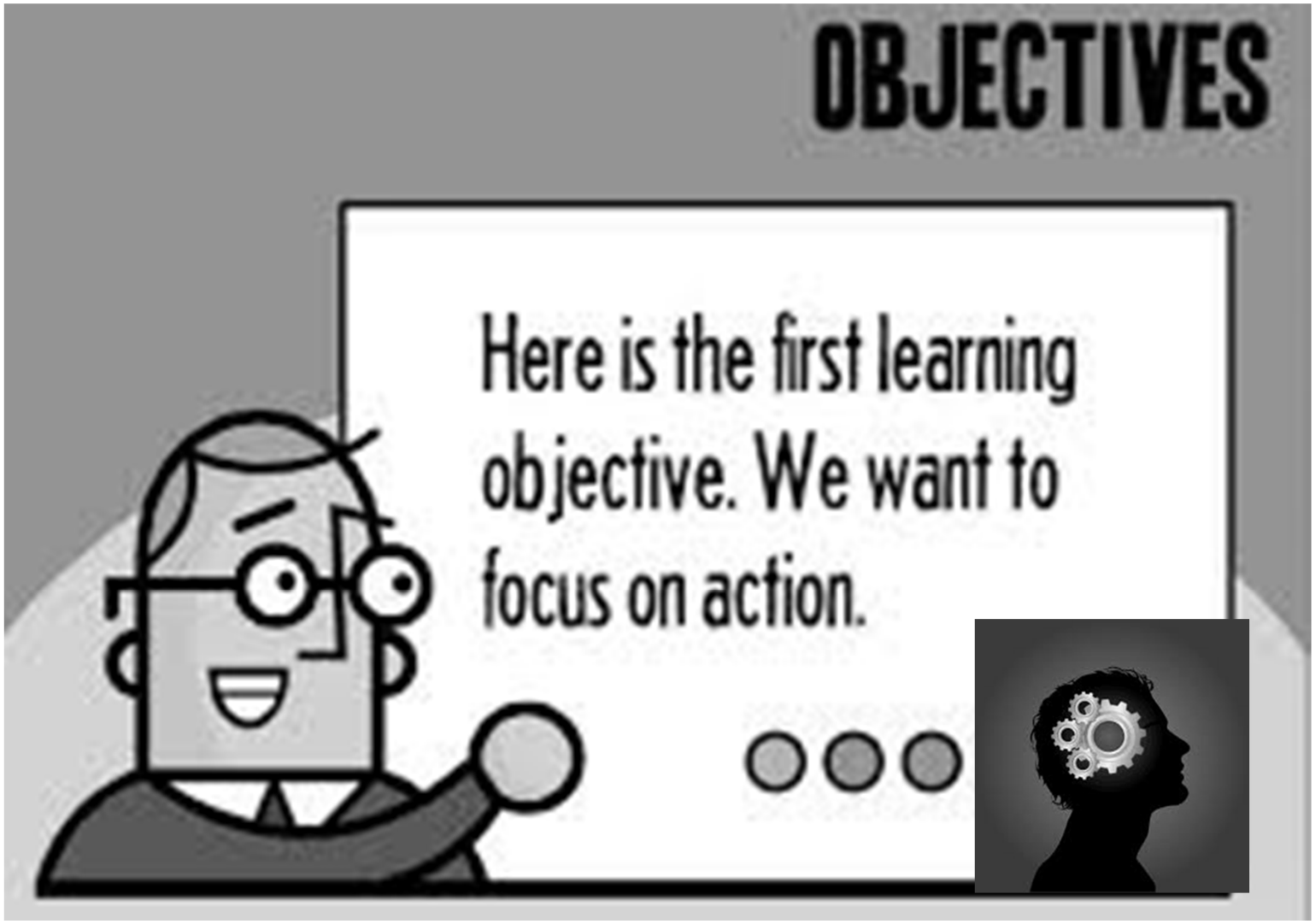
OBJECTIVES
Here is the first learning objective. We want to focus on action.

To

- To identify the different causative viruses.
- To identify the different clinical presentatations.
- To know the different modes of transmissions.
- To be able to make interpretation of serologic and molecular findings.
- To outline lines of management.

Acute hepatitis

- " Acute inflammation of the liver "
- It includes : Acute viral hepatitis.
- Alcoholic hepatitis.
- Autoimmune hepatitis.
- Ischemic hepatitis.
- Drug-induced hepatitis.

Acute viral hepatitis.

- Acute viral hepatitis (AVH) is a systemic infection predominantly affecting the liver. AVH is most often caused by viruses which are hepatotropic (hepatitis A, B, C, D and E). Whereas hepatitis A and E are self-limiting, infection with hepatitis C and less so with hepatitis B mainly become chronic.

- Other viral infections (non hepatotropic) may on occasion affect the liver (Epstein−Barr virus [EBV], cytomegalovirus (CMV) , Herpes Simplex, Coxsackie virus, Adenovirus).

Classification of the hepatitis viruses :

Virus	Genome	Acute hepatitis	Chronic hepatitis
HAV	RNA	+	-
HBV	DNA	+	+
HCV	RNA	+	+
HDV	RNA	+	+

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Virus	Genome	Acute hepatitis	Chronic hepatitis
HEV	RNA	+	-
Non A- E hepatitis			
HGV (hepatitis G virus)	RNA	-	-
TTV (transfusion- transmitted virus)	DNA	-	-

Acute Viral Hepatitis

(Elevated ALT almost always found)

Signs and Symptoms

- fatigue
- mild fever
- loss of appetite
- flu-like illness (prodromal)
- muscle/joint aches

- abdominal pain
- nausea and vomiting
- dark urine - light-colored stool
- yellow eyes and skin (jaundice)

Aversion to alcohol and cigarettes

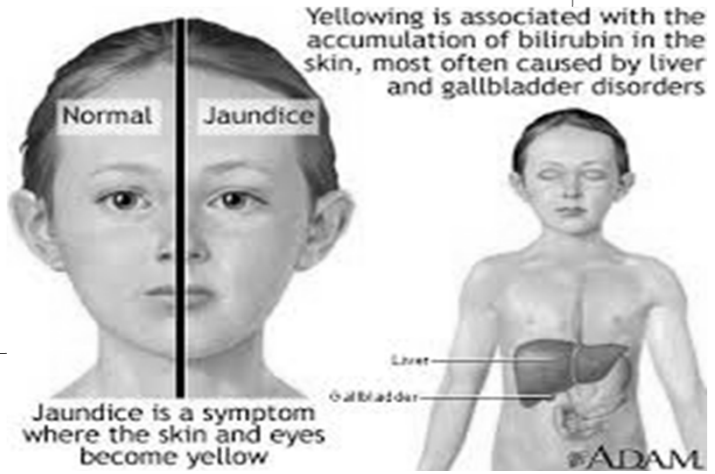
Acute hepatitis A :

- **Epidemiology of HAV**

- HAV is transmitted commonly most via the **fecal-oral route.** The Middle East has a particularly high prevalence of HAV infection. Most patients in these regions are infected when they are young children. Epidemics of HAV infection may be explained by **person-to-person contact**, such as occurs at institutions, or by exposure to a common source, such as **consumption of contaminated water or food.**

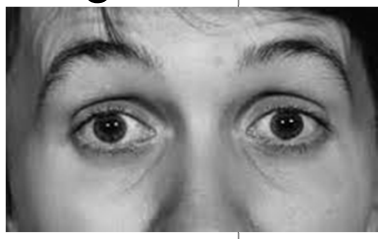
Natural history of HAV

The incubation period of HAV is 15-45 days (average 4 wk). The virus is excreted in stool during the first few weeks of infection, prior to the onset of symptoms. Young children who are infected with HAV usually remain asymptomatic. Acute hepatitis A is **more severe** and has higher mortality in **adults** than in children. The explanation for this is unknown.



Natural history of HAV

Typical cases of acute HAV infection are marked by several weeks of **malaise, anorexia, nausea, vomiting,** and **elevated aminotransferase** levels. **Jaundice** develops in more severe cases.



Some patients experience a **cholestatic hepatitis**, marked by the development of an elevated alkaline phosphatase level, in contrast to the classic picture of elevated aminotransferase levels. Other patients may experience several **relapses** during the course of a year. Less than 1% of cases result in **fulminant** hepatic failure.

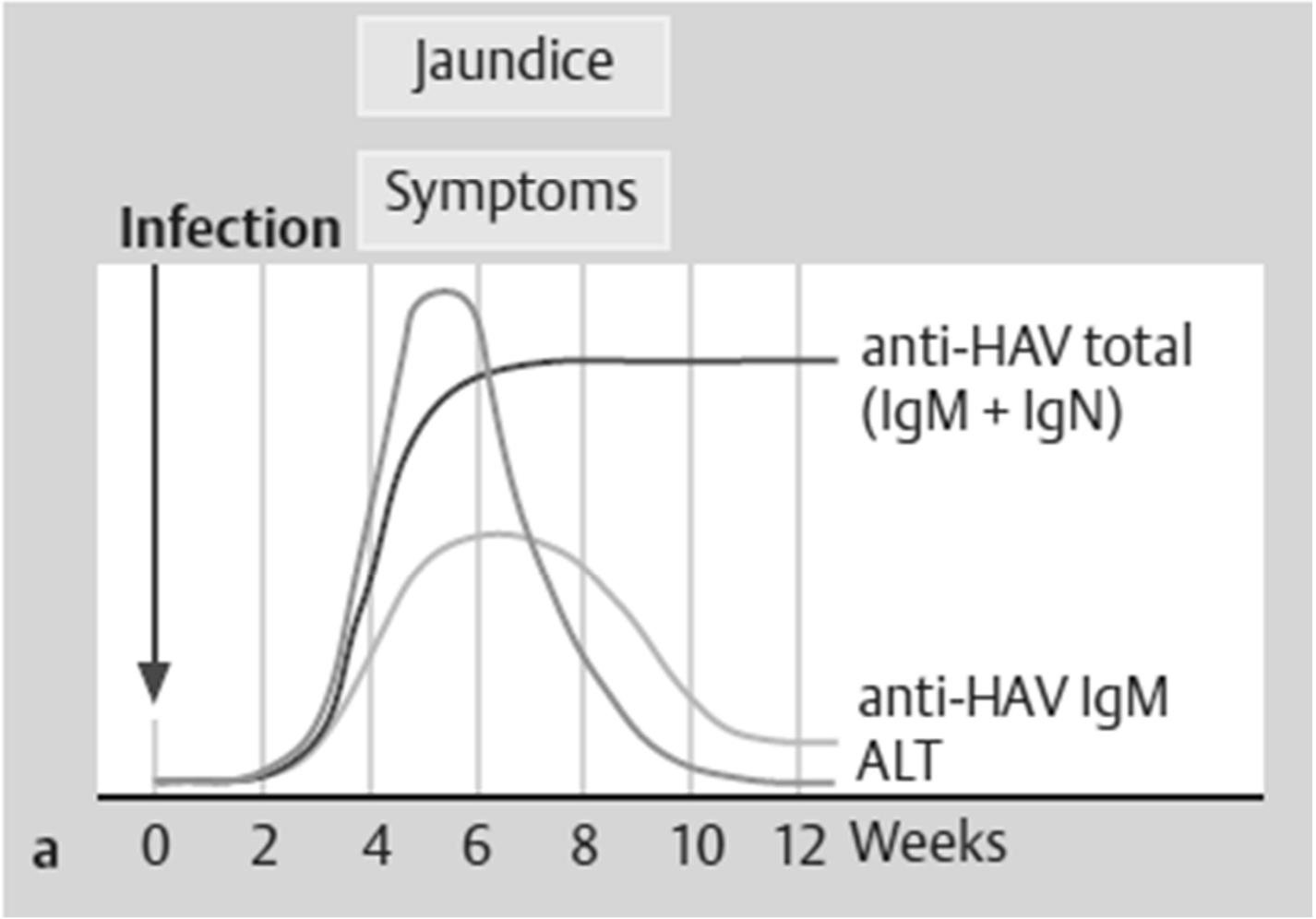
HAV infection does not persist and never causes chronic hepatitis.

Raised serum alanine transaminase (ALT) is the best indicator of acute hepatic injury but does not reflect disease severity (bilirubin and International Normalized Ratios (INR) are required for this, as they reflect deterioration in liver functions)

Diagnosis of hepatitis A

Acute infection is documented by the presence of immunoglobulin M (IgM) anti-HAV, which disappears several months after the initial infection. The presence of immunoglobulin G (IgG) anti-HAV merely demonstrates that an individual has been infected with HAV at some point in the past, from 2 months ago to decades ago. IgG anti-HAV appears to offer patients lifelong immunity against recurrent HAV infection.

Acute hepatitis A



Treatment for acute of HAV infection

Treatment for acute hepatitis caused by HAV is **supportive in nature because no antiviral therapy is available.**

Hospitalization is needed for patients whose nausea and vomiting places them at risk for dehydration. Patients with acute liver failure require close monitoring to ensure they do not develop fulminant hepatic failure.

Prevention of HAV infection

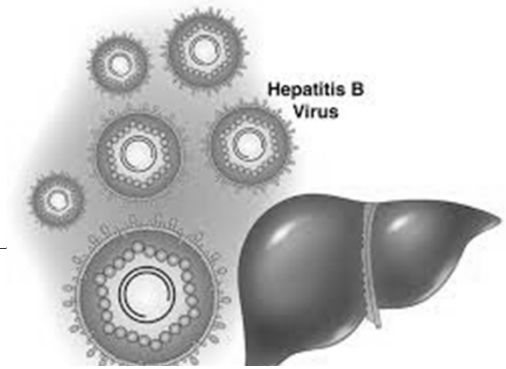
Prevention now recommend vaccination against HAV for individuals traveling to endemic regions, and vaccination is recommended for any patient with chronic liver disease. The HAV vaccines (inactivated), Havrix (GlaxoSmithKline; Research Triangle Park, NC) and Vaqta (Merck; Whitehouse Station, NJ), are 1-mL intramuscular injections (0.5 mL in children), **given more than 1 month before anticipated travel.** This results in a better-than-90% likelihood of stimulating production of IgG anti-HAV, with resulting immunity against HAV infection. **A booster dose of the vaccine is recommended 6 months after** the initial vaccination. Whether HAV vaccine administration should be mandated in children (as is HBV vaccination) remains unclear.

An alternative vaccine (HAV inactivated and HBV recombinant vaccines) is Twinrix (GlaxoSmithKline). This product is immunogenic against both HAV and HBV. Typical administration involves 3 injections of 1 mL given intramuscularly on a 0-, 1-, and 6-month schedule. The FDA has approved its use in adults.

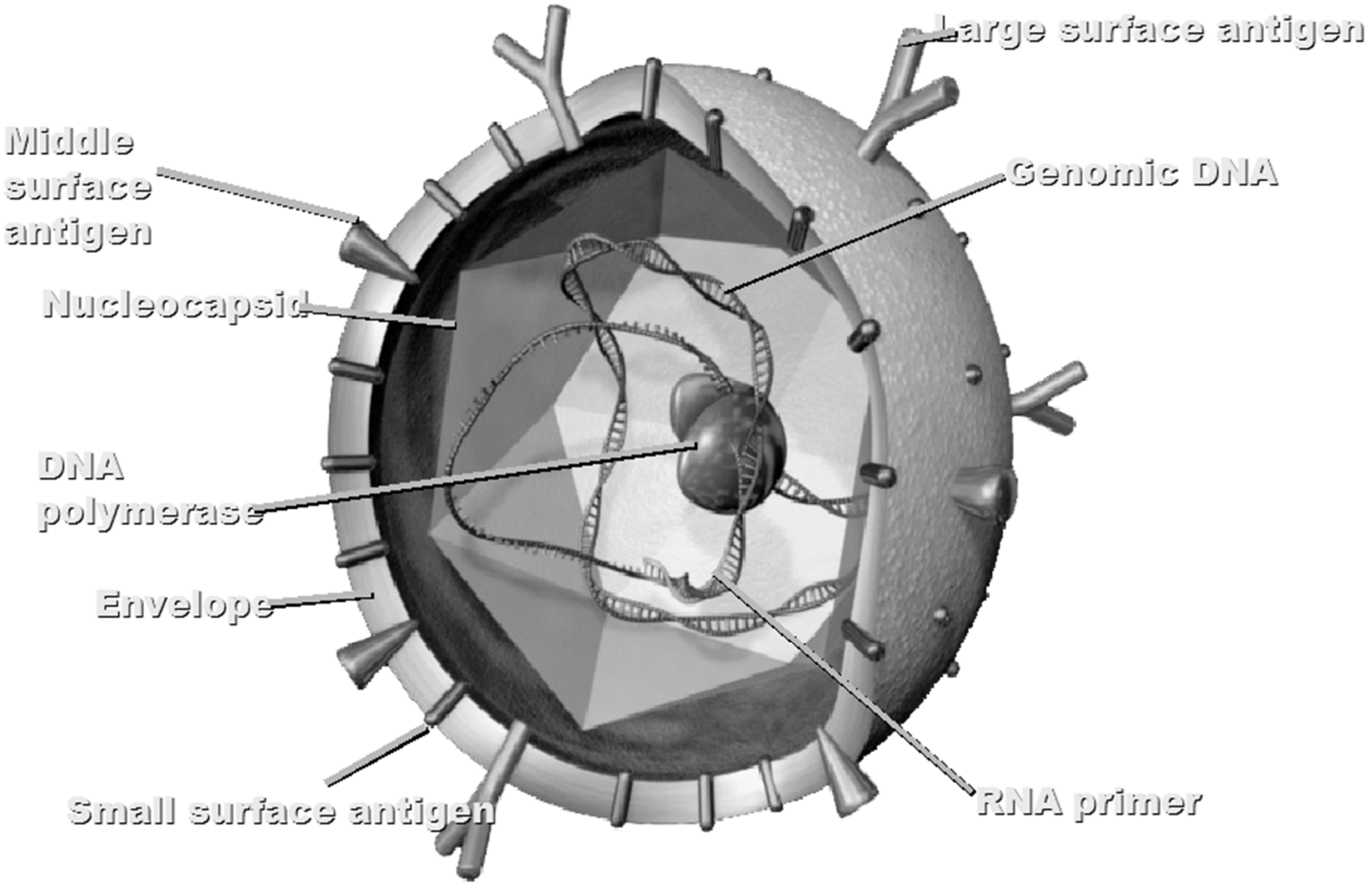
The administration of **hepatitis A immune globulin** is an alternative to vaccination against HAV infection. The dose is 0.02 mL/kg given intramuscularly for individuals who anticipate spending fewer than 3 months in an endemic region. Travelers should receive 0.06 mL/kg intramuscularly every 4-6 months if they are planning to spend more than 3 months in a region where HAV is endemic.

Hepatitis B :

HBV is a member of the Hepadnaviridae family. The viral core particle consists of a nucleocapsid, HBcAg, which surrounds HBV DNA, and DNA polymerase. The nucleocapsid is coated with HBsAg. **The intact HBV virion is known as the Dane particle**. Dane particles and spheres and tubules containing only **HBsAg** are found in the blood of infected patients. In contrast, **HBcAg** is not detected in the circulation. It can be identified by immunohistochemical staining of infected liver tissue.

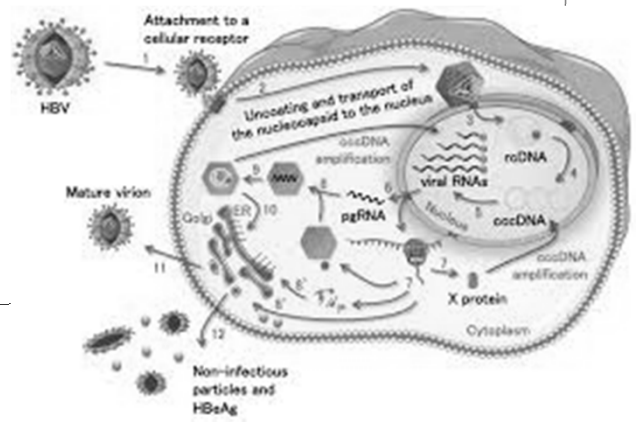


Hepatitis B virus



Mechanism of hepatocyte necrosis in HBV infection

HBV may be directly cytopathic to hepatocytes. However, immune system–mediated cytotoxicity plays a predominant role in causing liver damage. The immune assault is driven by human leukocyte antigen class I–restricted CD8 cytotoxic T lymphocytes that recognize HBcAg and HBeAg on the cell membranes of infected hepatocytes.



Transmission of HBV

HBV is readily detected in serum. It is seen at very low levels in semen, vaginal mucus, saliva, and tears. The virus is not detected in urine, stool, or sweat. HBV can survive storage at -20°C (-4°F) and heating at 60°C (140°F) for 4 hours. It is inactivated by heating at 100°C (212°F) for 10 min or by washing with sodium hypochlorite (bleach).


Body Piercing


Tattooing

Causes of
Hepatitis B


Vertical Transmission


Blood Transfusion

Perinatal transmission of HBV

The vast majority of HBV cases around the world result from perinatal transmission. Infection appears to be due to contact with a mother's infected blood at the time of delivery, as opposed to transplacental passage of the virus. Neonates infected via perinatal infection are usually asymptomatic. Although breast milk can contain HBV virions, the role of breastfeeding in transmission is unclear.

Sporadic cases of hepatitis B

The cause of HBV infection is unknown in approximately 27% of cases. Some these cases, in fact, may be due to sexual transmission or contact with blood.

Sexual transmission of HBV

HBV is transmitted more easily than HIV or HCV. Infection is associated with vaginal intercourse, genital-rectal intercourse, and oral-genital intercourse. An estimated 30% of sexual partners of patients infected with HBV also contract HBV infection. However, HBV cannot be transmitted through kissing, hugging, or household contact such as sharing towels, eating utensils, or food. Sexual activity is estimated to account for as many as 50% of HBV cases in the United States.

Parenteral transmission of HBV

HBV was once a common cause of posttransfusion hepatitis. Screening of US blood donors for HBcAb, beginning in the early 1970s, dramatically reduced the rate of HBV infection associated with blood transfusion. Patients with hemophilia, those on renal dialysis, and those who have undergone organ transplantations remain at increased risk of infection.

Intravenous drug use accounts for 20% of US cases of HBV. A history of HBV exposure is identified in approximately 50% of persons who use intravenous drugs.

The risk of acquiring HBV after a needle stick from an infected patient is estimated to be as high as 5%.

Epidemiology of HBV

Approximately 90-95% of neonates with acute infection and 5% of adults with acute infection develop chronic HBV infection. Infection with HBV is defined by the presence of HBsAg more than 6 months.

The infection clears in the remainder of patients, and these patients develop a life-long immunity against repeated infections. Approximately 5% of the world's population (ie, 300 million people) is chronically infected with HBV. More than 10% of people living in sub-Saharan Africa and in East Asia are infected with HBV.

Maintenance of a **high HBsAg carriage** rate in these parts of the world is partially explained by the high prevalence of perinatal transmission and by the low rate of HBV clearance by neonates.

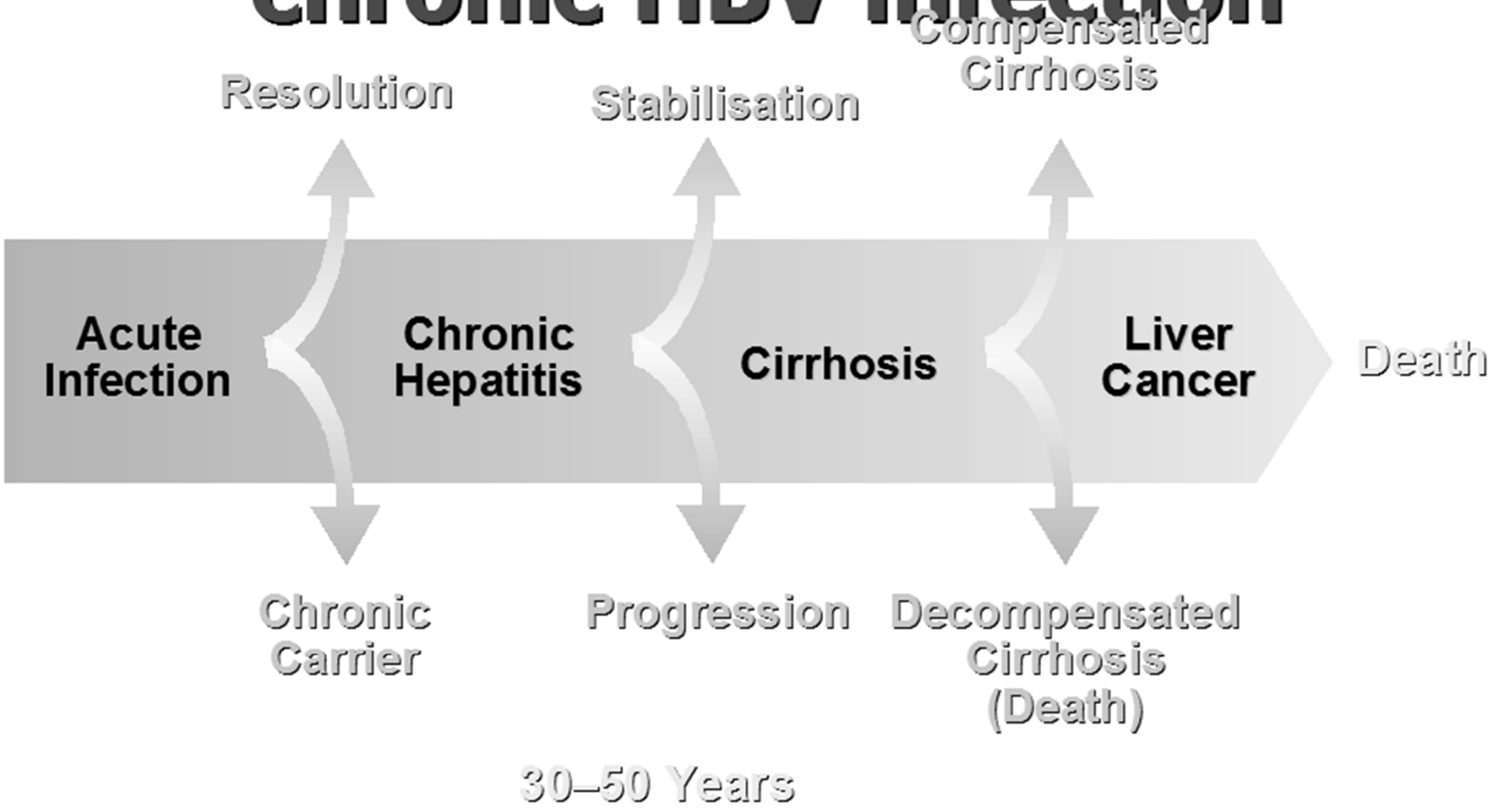
20%of chronic HBV infection cases progress to cirrhosis or hepatocellular carcinoma (HCC), resulting in more than 1 million deaths each year. This makes hepatitis B the ninth leading cause of death in the world.

Natural history of HBV

The incubation period of HBV is 40-150 days, with an average of approximately 12 weeks. As with HAV, the clinical illness associated with acute HBV infection may range from mild disease to a disease as severe as fulminant hepatic failure (<1% of patients).

After acute hepatitis resolves, 95% of adult patients and 5-10% of infected infants ultimately develop anti-HBV antibody, clear HBsAg (and HBV virions), and fully recover. **Five percent of adult patients and 90-95% of infected infants develop chronic infection.**

Natural history of chronic HBV infection



Adapted from Feitelson, *Lab Invest* 1994

Diagnosis of acute self-limited HBV infection.

- HBsAg is the first serum marker seen in persons with acute infection. It represents the presence of HBV virions (Dane particles) in the blood.

- HBeAg, a marker of viral replication, is also present. When viral replication slows, HBeAg disappears and anti-HBe is detected. Anti-HBe may persist for years.

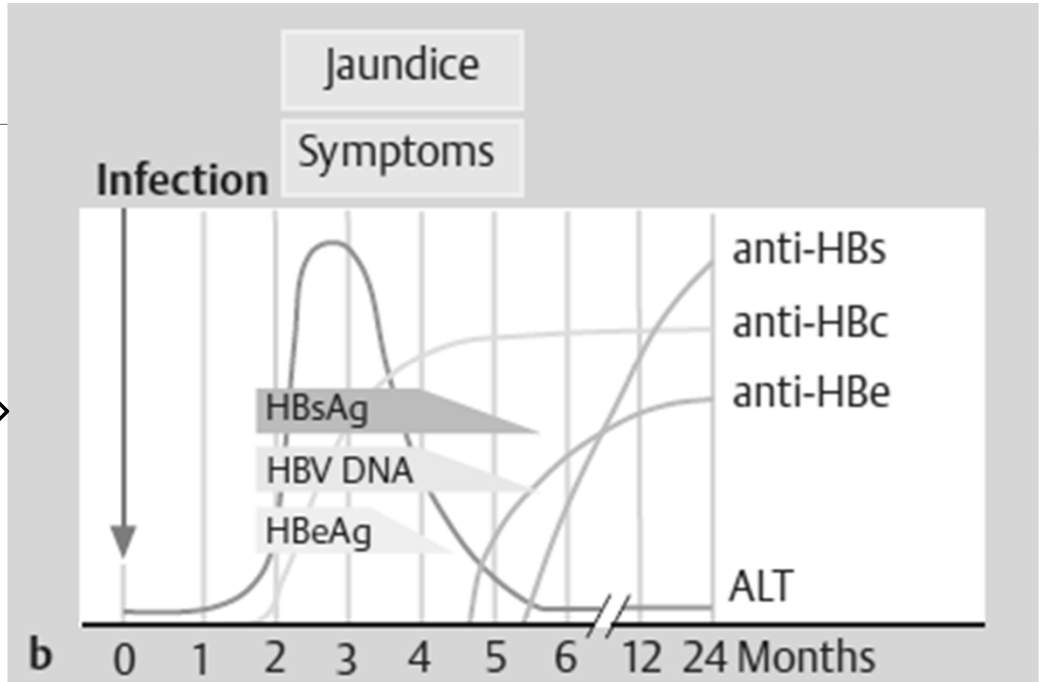
- The first antibody to appear is anti-HBc (HBcAb). Initially, it is of the IgM class. Indeed, the presence of IgM anti-HBc is diagnostic for acute HBV infection.

Diagnosis of acute self-limited HBV infection

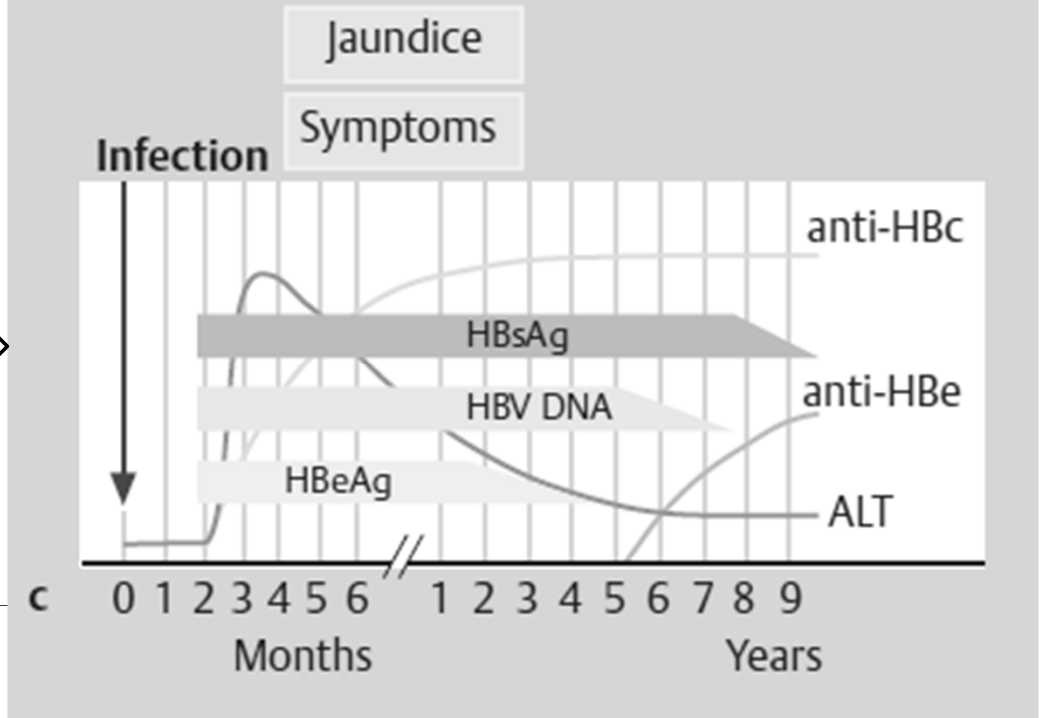
- Weeks later, IgM anti-HBc disappears and IgG anti-HBc is detected. Anti-HBc may be present for life. The anti-HBc (total) assay detects both IgM and IgG antibodies. The presence of anti-HBc (total) demonstrates that the patient has had a history of infection with HBV at some point in the past.

- In patients who clear the HBV, HBsAg usually disappears 4-6 months after infection, as titers of anti-HBs (HBsAb) become detectable. Anti-HBs is believed to be a neutralizing antibody, offering immunity to subsequent exposures to HBV. Anti-HBs may persist for the life of the patient.

Acute hepatitis B



Chronic hepatitis B



Knowing key points helps in the interpretation of serology findings in acute HBV infection.

- The presence of HBsAg does not indicate whether the infection is acute or chronic.
- The presence of anti-HBc (IgM) is the sine qua non of acute HBV infection.
- The presence of anti-HBc (total) indicates that a patient has been infected with HBV at some point. The anti-HBc (total) remains positive both in patients who clear the virus and in patients with persistent infection.

The presence of anti-HBc (total) with a negative HBsAg and a negative anti-HBs indicates 1 of 4 things.

- **First, the test result is a false positive.**
- **Second, the patient is in a window of acute hepatitis, between the elimination of HBsAg and the appearance of anti-HBs. This scenario is not observed in patients with chronic HBV infection.**
- **Third, the patient has cleared the HBV virus but has lost anti-HBs over the years.**
- **Fourth, the patient is one of the uncommon individuals with active HBV replication who is negative for HBsAg. This situation is diagnosed when either a positive HBeAg or a positive HBV DNA result is found; ‘ occult HBV infection’.**

Treatment of acute hepatitis B

As with the treatment of acute hepatitis A, no well-established antiviral therapy is available for acute HBV infection. Supportive treatment recommendations are the same as for acute hepatitis A. Whether lamivudine, adefovir dipivoxil, or other antiviral therapies have an impact on the natural history of severe cases of acute HBV infection remains unclear. However, one recent study (Schmilovitz-Weiss H et al) described a rapid clinical and biochemical response in 13 of 15 patients with severe acute hepatitis B who received lamivudine

HBV vaccine

Plasma-derived and recombinant HBV vaccines use HBsAg to stimulate the production of anti-HBs in non-infected individuals. The vaccines are highly effective, with a greater than 95% rate of seroconversion. Vaccine administration is recommended for all infants and for adults at high risk of infection (eg, those receiving dialysis, healthcare workers).

The recommended vaccination schedule for infants is an initial vaccination at the time of birth (ie, before hospital discharge), repeat vaccination at 1-2 months, and another repeat vaccination at 6-18 months. The recommended vaccination schedule for adults is an initial vaccination, a repeat vaccination at 1 month, and another repeat vaccination at 6 months.

Postexposure prophylaxis

Hepatitis B immune globulin (HBIG) is derived from plasma. It provides passive immunization for individuals who describe recent exposure to a patient infected with HBV. HBIG is also administered following liver transplantation to persons infected with HBV, in order to prevent HBV-induced damage to the liver allograft. Recommendations for postexposure prophylaxis for contacts of patients positive for HBsAg are as follows:

- Perinatal exposure - HBIG plus vaccination at time of birth (90% effective)
- Sexual contact with an acutely infected patient - HBIG plus vaccination
- Sexual contact with a chronic carrier - Vaccination

Hepatitis C :

- HCV is a Flavivirus. It is a 9.4-kb RNA virus with a diameter of 55 nm. It has one serotype and multiple genotypes. HCVs have profound genetic variability throughout the world. At least 6 major genotypes and more than 80 subtypes are described, with as little as 55% genetic sequence homology. Genotype 1b is the genotype most commonly seen in the United States, in Europe, in Japan, and in Taiwan. Genotypes 1b and 1a (also common in the United States) are thought to be less responsive to interferon therapy than other HCV genotypes. Genotype 4 is common in Egypt.

Transmission of HCV via blood transfusion

Screening of the US blood supply has dramatically reduced the incidence of transfusion-associated HCV infection. Before 1990, 37-58% of cases of acute HCV infection (then known as NANB) were attributed to the transfusion of contaminated blood products. Now, only approximately 4% of acute cases are attributed to transfusion. Acute hepatitis C remains an important issue in dialysis units, where patients' risk for HCV infection is approximately 0.15% per year.

Transmission of HCV via intravenous and intranasal drug use

Intravenous drug use remains an important mode of transmitting HCV. Intravenous drug use and the sharing of paraphernalia used in the intranasal snorting of cocaine and heroin account for approximately 60% of new cases of HCV infection. More than 90% of patients with a history of intravenous drug use have been exposed to HCV.

Transmission of HCV via occupational exposure

Occupational exposure to HCV accounts for approximately 4% of new infections. On average, the chance of acquiring HCV after a needle stick injury involving an infected patient is 1.8% (range, 0-7%). Of importance, reports of HCV transmission from healthcare workers to patients are extremely uncommon.

Transmission of HCV via sexual contact

Approximately 20% of cases of hepatitis C appear to be due to sexual contact. In contrast to hepatitis B, approximately 5% of the sexual partners of those infected with HCV contract hepatitis C. Current guidelines do not recommend the use of barrier precautions for patients with a steady sexual partner. However, patients should avoid sharing razors and toothbrushes with others. In addition, contact with patients' blood should be avoided.

Transmission of HCV via perinatal transmission

Perinatal transmission appears to be uncommon. It is observed in fewer than 5% of children born to mothers infected with HCV. The risk of perinatal transmission of HCV is higher, estimated at 18%, in children born to mothers co-infected with HIV and HCV. Available data show no increase in HCV infection in babies who are breastfed. The US Public Health Service does not advise against pregnancy or breastfeeding for women infected with HCV.

Natural history of acute hepatitis C

HCV has a viral incubation period of approximately 8 weeks. Most cases of acute HCV infection are asymptomatic. Even when symptomatic, the course of acute HCV infection tends to be mild, with aminotransferase levels rarely higher than 1000 U/L. Whether acute HCV infection is a cause of fulminant hepatic failure remains controversial.

Approximately 15% of patients acutely infected with HCV lose virologic markers for HCV. Thus, approximately 85% of newly infected patients remain viremic and may develop chronic liver disease. In chronic hepatitis, patients may or may not be symptomatic, with fatigue being the predominant reported symptom.

Aminotransferase levels may fluctuate from the reference range (<40 U/L) to 300 U/L. However, no clear-cut association exists between aminotransferase levels and symptoms or risk of disease progression

Diagnosis of hepatitis C using serologic tests for HCV

Structural and nonstructural regions of the HCV genome have been synthesized. These can be recognized by human IgG anti-HCV. Recombinant HCV antigens are used in enzyme-linked immunosorbent assay (ELISA) to detect anti-HCV in patients' sera. Anti-HCV test results remain negative for several months following acute HCV infection. After its appearance, the anti-HCV usually remains present for the life of the patient. This occurs even in the 15% of cases in which the patient clears the virus and does not develop chronic hepatitis. Anti-HCV is not a protective antibody and does not guard against future exposures to HCV.

Recombinant immunoblot assays (RIBAs) use recombinant HCV antigens that are fixed to a solid substrate. They are more specific than ELISA testing and have been used to confirm positive ELISA results. However, their use is being abandoned in favor of HCV RNA testing.

Diagnosis of hepatitis C using HCV RNA tests

PCR assays and branched DNA assays have been used since the early 1990s to detect HCV RNA in serum. In contrast to ELISA and RIBA testing, HCV RNA testing can confirm the presence of active HCV infection.

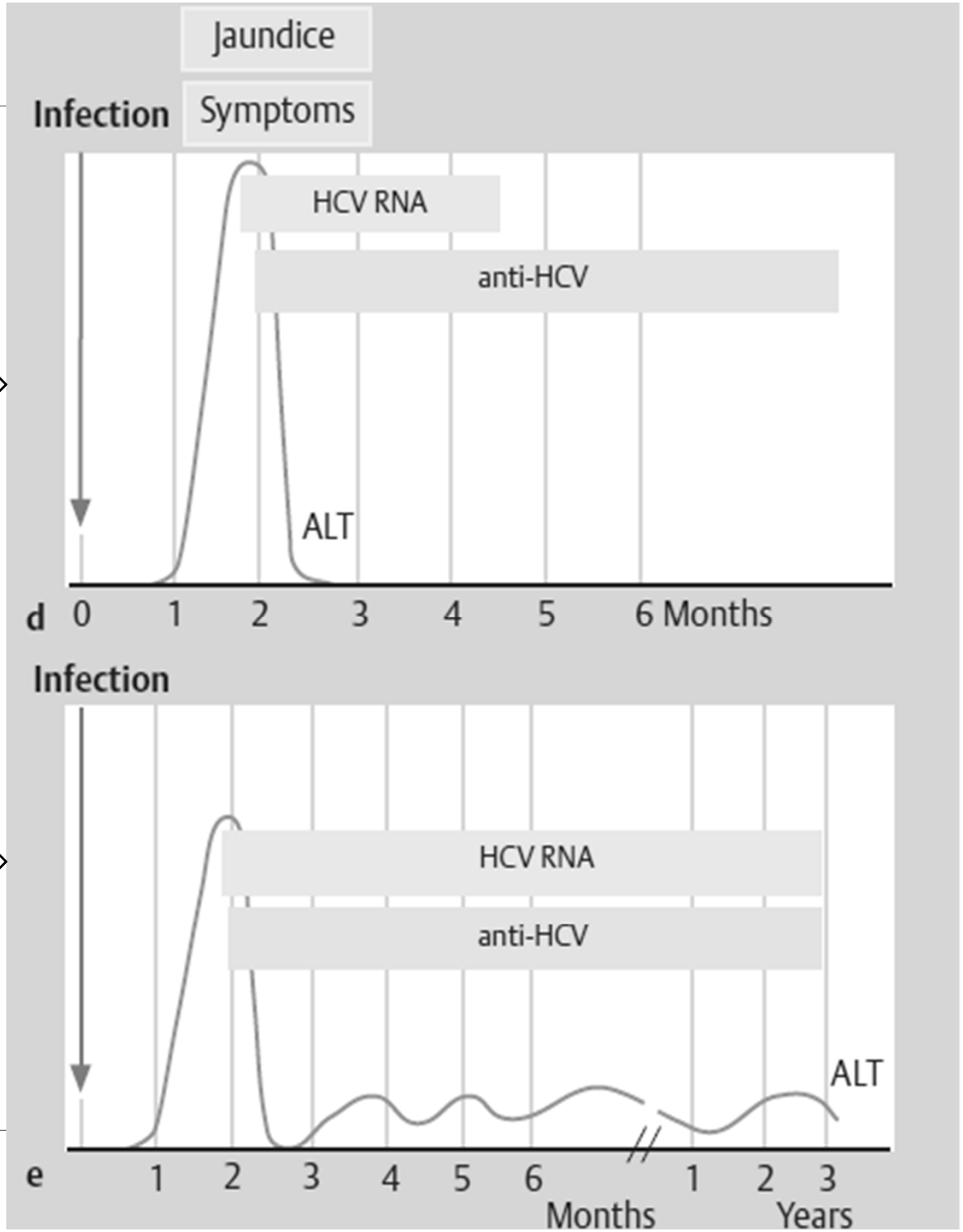
HCV RNA testing has a number of important uses. It aids in the diagnosis of (1) early cases of HCV infection, prior to the development of HCV antibody positivity or an elevation of the ALT level; (2) seronegative cases, such as in the setting of end-stage renal disease; and (3) cases of perinatal transmission.

Diagnosis of hepatitis C using HCV RNA tests

HCV RNA testing also helps to (1) confirm false-positive cases, such as autoimmune hepatitis; (2) assess the HCV genotype and viral load; (3) predict the response to interferon therapy; (4) guide the duration and dose of interferon therapy; and (5) assess the likelihood of relapse following a response to interferon therapy

Acute hepatitis C

Chronic hepatitis C



Treatment of acute hepatitis C

Acute hepatitis C is detected infrequently. When it is identified, early therapy with interferon should be considered. In one recent article, 44 patients with acute hepatitis C were treated with interferon alfa-2b at 5 million U/d subcutaneously for 4 weeks and then 3 times per week for another 20 weeks. About 98% of patients developed a sustained virologic response .

Hepatitis D :

- HDV is a single-stranded, 1.7-kb RNA virus. The viral particle is 36 nm in diameter and contains HDAg and the RNA strand. It uses HBsAg as its envelope protein. Thus, HBV co-infection is necessary for the packaging and release of HDV virions from infected hepatocytes.
- **Epidemiology of HDV**
- HDV is believed to infect approximately 5% of the world's 300 million HBsAg carriers. The prevalence of HDV infection in South America and Africa is high. Italy and Greece are areas of intermediate endemicity and are well studied. The sharing of contaminated needles in intravenous drug use is thought to be the most common means of transmitting HDV. Persons who use intravenous drugs who are also positive for HBsAg have been found to have HDV prevalence rates ranging from 17-90%. Sexual and perinatal transmissions are also described.

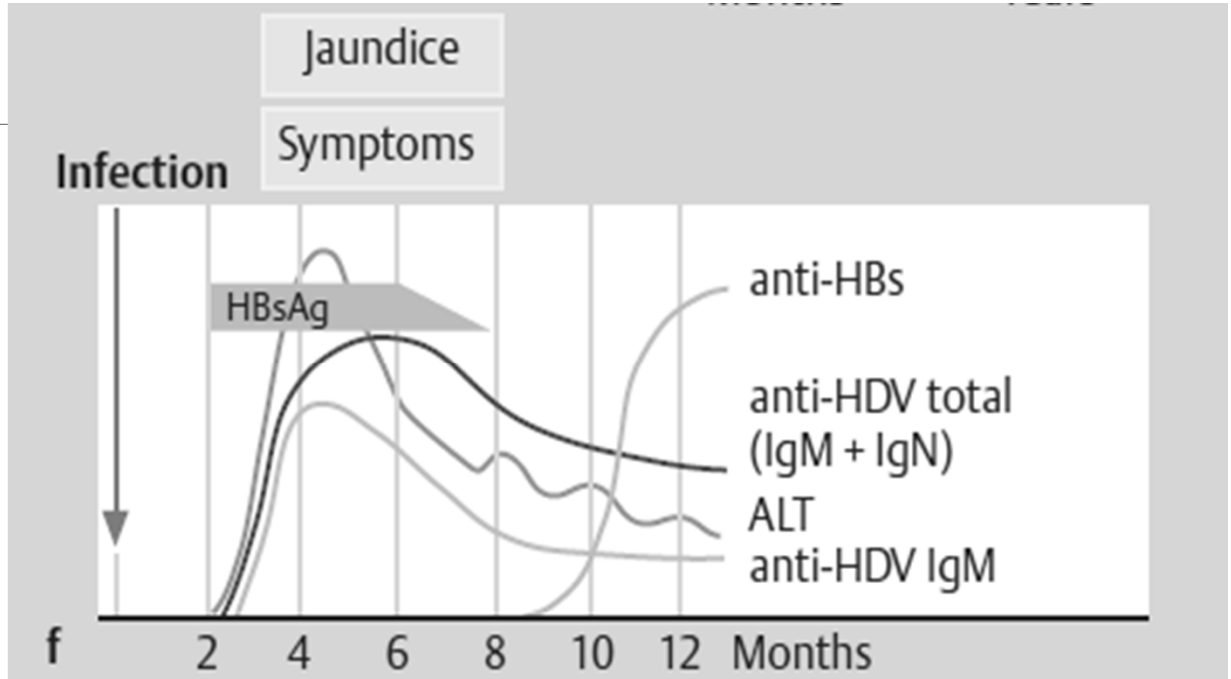
Natural history of HDV co-infection

Simultaneous introduction of HBV and HDV into a patient results in the same clinical picture as acute infection with HBV alone . The resulting acute hepatitis may be mild or severe. Similarly, the risk of developing chronic HBV and HDV infection after acute exposure to both viruses is the same as the rate of developing chronic HBV infection after acute exposure to HBV (approximately 5% in adults). However, chronic HBV and HDV disease tends to progress more rapidly to cirrhosis than chronic HBV infection alone.

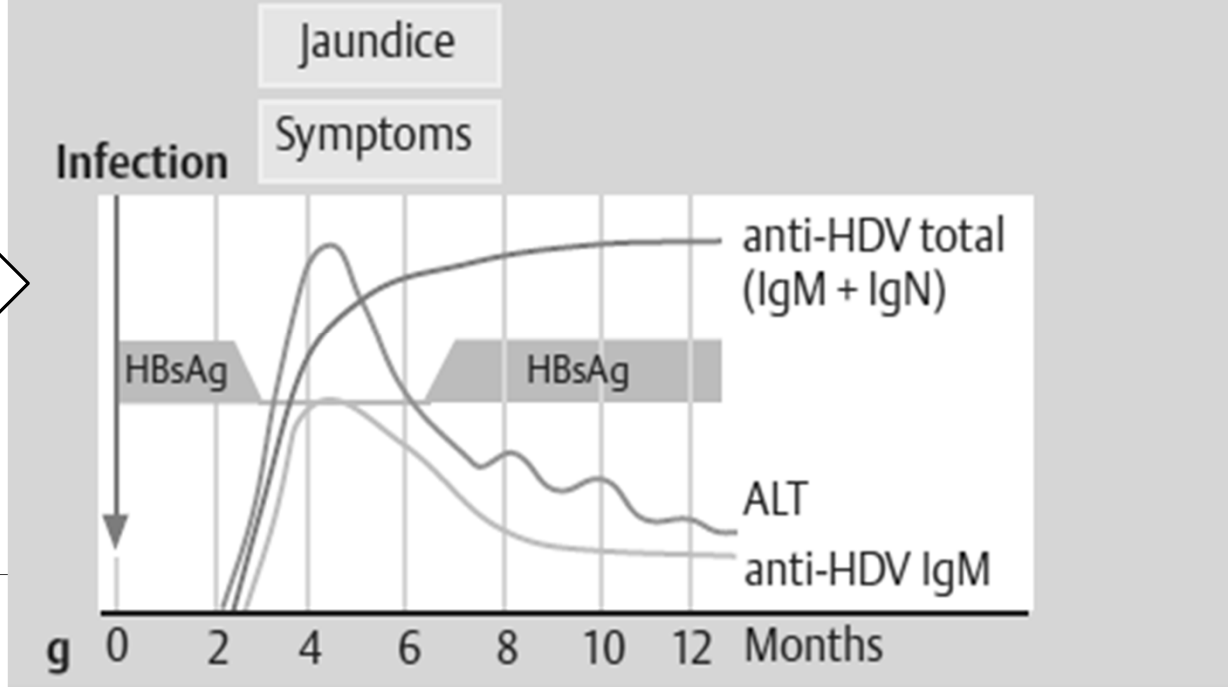
Natural history of HDV superinfection

Introduction of HDV into an individual already infected with HBV may have dramatic consequences. Superinfection may give HBsAg-positive patients the appearance of a sudden worsening or flare of hepatitis B. HDV superinfection may result in fulminant hepatic failure.

HBV/HDV coinfection



HBV/HDV superinfection



Diagnosis of HDV infection

A serologic diagnosis of HDV infection is made by using IgM anti-HDV and IgG anti-HDV tests. HBcAb IgM should be used to help distinguish between co-infection (HBcAb IgM–positive) and superinfection (HBcAb IgM–negative). Detecting HDV RNA in serum is also possible.

Treatment of hepatitis D

Patients co-infected with HBV and HDV are less responsive to interferon therapy than patients infected with HBV alone. To date, lamivudine appears to be ineffective against HBV/HDV co-infection.

Hepatitis E :

- **Epidemiology of HEV**
- HEV is transmitted via the fecal-oral route. HEV appears to be endemic in some parts of the lesser-developed countries. Anti-HEV antibodies are observed in as many as 60% of Indian children younger than 5 years.
- **Natural history of HEV**
- HEV primarily infects adults and young adults. Acute infection is generally less severe than acute HBV infection and is characterized by fluctuating aminotransferase levels. However, pregnant women, especially when infected during the third trimester, have up to a 25% risk of mortality associated with acute HEV infection. HEV does not appear to cause chronic liver disease.

Diagnosis of HEV infection

The serologic diagnosis is made by using IgM anti-HEV and IgG anti-HEV. HEV RNA can be detected in the serum and stool of infected patients.

Treatment of hepatitis E

The treatment of those infected with HEV is supportive in nature.

Golden pearls in diagnosis

Acut viral Hepatitis A-E

	Hepatitis A	Hepatitis B	Hepatitis C	Hepatitis D	Hepatitis E
Virus	HAV RNA	HBV DNA	HCV RNA	HDV RNA	HEV RNA
Screening procedure	anti-HAV	HBsAg or anti-HBc	anti-HCV	anti-HDV	anti-HEV
Transmission	enteral	parenteral, sexual, perinatal	parenteral	parenteral	enteral
Incubation period (days)	15–49	25–160	21–84	60–110	10–56
Acute hepatitis	+	+	+	+	+
Fulminant hepatitis	very rare	rare (approx. 1%)	very rare	occasional	rare (20% during pregnancy)
Chronic hepatitis [%]	–	1–10	55–85	2–7 in coinfection, >70 in superinfection	–
Cirrhosis in chronic hepatitis [%]	–	approx. 20–30	approx. 4–20	approx. 30–60	–
HCC	–	+	+	+	–

Hepatitis viruses: interpretation of serologic and molecular findings

Virus	Marker	Interpretation
HAV	anti-HAV IgM	acute HAV infection
	anti-HAV IgG	resolved HAV infection and immunity against reinfection or, vaccination response
HBV	HBsAg	HBV infection
	HBeAg	replicative HBV infection
	anti-HBc IgM	acute or chronic HBV infection
	anti-HBc IgM + IgG	chronic HBV infection
	anti-HBc IgG	active or resolved HBV infection
	HBsAg + anti-HBe	nonreplicative HBV infection, replicative infection with HBV mutants
	anti-HBs + anti HBe	resolved HBV infection, anti-HBV immunity
	anti-HBs	resolved HBV infection and immunity against reinfection or, vaccination response
	HBV DNA	replicative HBV infection
HCV	anti-HCV	active or resolved HCV infection
	HCV RNA	replicative HCV infection
HDV	anti-HDV IgM	acute HDV infection
	anti-HDV IgM + IgG	chronic HDV infection
	anti-HDV IgG	resolved HDV infection
	HDV RNA	replicative HDV infection
HEV	anti-HEV	acute or resolved HEV infection
	HEV RNA	replicative HEV infection


BEST WISHES